QUANTITATIVE MEASUREMENT OF REGIONAL CIRCULATION IN THE CENTRAL NERVOUS SYSTEM BY THE USE OF RADIOACTIVE INERT GAS

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I. INTRODUCTION

The method to be described is one which permits quantitative determinations of blood flow in the gross structures of the central nervous system. Other available quantitative methods for measuring cerebral blood flow, e.g., the nitrous oxide technique (12, 15) and its modifications (11, 18, 19, 20, 23) or the various tracer dilution techniques (7, 12, 21), apply only to the brain as a whole. Observations of the circulation in specific areas of the brain have been made by means of capillary counting techniques (2), direct visualization of the superficial cerebral or pial vessel (4, 5), or by locally placed thermoelectric devices (6, 24, 25), but these methods are neither quantitative nor applicable to more than a few limited areas at the same time. Most of these limitations are avoided by the recently developed radioactive inert gas technique (14, 17). By means of it,

the rate of blood flow in numerous superficial and deep structures of the
brain and spinal cord of the cat have been simultaneously and quantita-
tively measured under conditions that approximate the physiological state
(27). On the other hand, it is subject to one serious disadvantage. Since
each set of measurements requires the sacrifice of the animal, repeat deter-
minations in the same preparation are impossible, and the method is not
applicable to man.

It is the purpose of this article to develop the theoretical basis of the
method, to describe the procedures followed in its application, and to
present the results obtained with it in several studies of the physiology
and pharmacology of the local cerebral circulation.

II. METHOD

1. Theory

The method for the quantitative measurement of regional cerebral
circulation is based upon the principles which govern the exchange of a
biologically inert gas between the blood and tissues. These principles have
been extensively reviewed by Kety (13).

For a biologically inert diffusible tracer substance, i.e., one which is
neither utilized nor produced in the tissues under study, the time rate of
change of the amount of tracer substance within the tissues is equal to the
difference in the rates at which it is brought to the tissues in the arterial
blood and removed from them in the venous blood. This restatement of
the law of conservation of mass, widely known in circulatory physiology
as the Fick principle, can be expressed mathematically as follows:

$$\frac{dQ_i}{dt} = F(C_a - C_v) \tag{1}$$

in which Q_i is the quantity of tracer and F the rate of blood flow in the
tissues, t equals time, and C_a and C_v are the tracer concentrations in the
arterial blood and in the venous drainage representative of the tissues,
respectively.

By dividing both sides of the equation by W, the weight of the tissue
in which the tracer is distributed, Eq. (1) becomes:

$$\frac{dC_i}{dt} = \frac{F(C_a - C_v)}{W} \tag{2}$$

in which C_i is the tracer concentration and F/W is the blood flow rate, both
per unit weight of tissue.

For a tissue which is homogeneous as regards its blood perfusion rate
and the solubility of the tracer material within it, Kety (13) has derived

the following relationship between the arterial-venous and the arterial-tissue concentration differences:

$$(C_a - C_v) = m(C_a - C_i/\lambda) \tag{3}$$

in which λ is the tissue:blood partition coefficient for the tracer material, and m equals a constant between 0 and 1 which represents the net effects of diffusion limitations, capillary impermeability, arteriovenous shunts, and all other factors which tend to limit the equilibration of the tissue with the blood perfusing it. In the absence of such limitations, m equals unity, and Eq. (3) resolves to:

$$C_v = (C_i/\lambda) \tag{4}$$

In other words, under such conditions the concentration of the tracer material in the representative venous blood remains in constant equilibrium with that of the tissue which it drains; indeed, it is equal to it after correction by the relative solubilities of the tracer in the two media. Combining Eqs. (2) and (4) then leads to the following expressions:

$$\frac{dC_i}{dt} = \frac{F(C_a - C_i/\lambda)}{W} \tag{5}$$

or

$$\frac{dC_i}{dt} = \frac{F(\lambda C_a - C_i)}{\lambda W} \tag{6}$$

Since $F/\lambda W$ is a constant incorporating the rate of blood flow per unit weight of tissue and the partition coefficient of the tracer between the tissue and blood, Eq. (6) is a simple differential equation of the first order and first degree. When integrated between the limits of zero time and time T, a given time after the onset of circulation of the tracer substance, it becomes:

$$\frac{(C_i)_T}{\lambda} = k \int_0^T C_a e^{-k(T-t)} \, dt \tag{7}$$

in which $(C_i)_T$ is the concentration of the tracer in the tissue at time T, and $k = F/\lambda W$.

As previously pointed out, several assumptions are required in the derivation of Eq. (7). First, it is necessary that the equilibration of the tissue with the blood as regards the concentration of the tracer be limited only by the blood flow and not by the diffusion of the tracer through the capillary walls and throughout the extravascular tissues. There is considerable theoretical and experimental evidence to indicate that inert gases and water (deuterium oxide) are sufficiently freely diffusible between blood

and tissues to satisfy this requirement when they are employed as the
tracer material (10, 13). Secondly, it must be assumed that there are no
arteriovenous shunts or capillary bypasses in the tissues being studied.
It is generally believed on the basis of a number of anatomical studies
that no such shunts exist in the brain (1, 22). Finally, Eq. (7) applies only
to those tissues which are homogeneous with respect to the blood per-
fusion rate and the solubility of the tracer substance. It is assumed that
satisfaction of this requirement is approached by limiting the measure-
ments of blood flow to small anatomically discrete structures of the cen-
tral nervous system, which is, indeed, the ultimate purpose of the method.

Equation (7) provides the basis of the method and defines the variables
to be measured in order for regional cerebral blood flow to be determined.
It is apparent from it that blood flow per unit weight of tissue, e.g., F/W,
can be calculated if the following data are known: (1) the curve describing
the arterial concentration of the tracer from the time of its appearance in
the blood until a specific subsequent time T; (2) the concentration of the
tracer in the tissue at time T; and (3) the tissue:blood partition coefficient
of the tracer substance at body temperature. The experimental procedure
is designed to obtain these data.

2. Procedure

a. Choice and Preparation of Radioactive Gas. Because the validity of
the method is dependent on the assumptions of diffusion equilibrium
between tissue and blood and the inertness of the tracer, a freely diffusible,
inert substance is necessary. These conditions are best met by an inert
gas. Furthermore, the use of a radioactive tracer greatly facilitates the
measurements of the variables required by Eq. (7). The radioactive gas,
I^{131}-tagged trifluoroiodomethane, CF_3I^{131}, has been employed in the ex-
periments thus far and found to be quite satisfactory. It is inert and radio-
active, and the β and γ emanations of the I^{131} are well suited to the tech-
niques which have been employed for their measurement in blood and
tissues. Since the gas is not commercially available, it is synthesized from
radioactive iodide by a method developed by Durell (3). Radioactive
elemental iodine, obtained from the oxidation of radioactive iodide by
dichromate, is incubated with stable trifluoroiodomethane at 220°C. for
2 hours. The stable trifluoroiodomethane is synthesized by the method
of Henne and Finnegan (9). During the incubation, an exchange of radio-
active iodine atoms with the stable iodine atoms in the gas molecules occurs
to form radioactive CF_3I^{131}. The gas is then purified of free radioactive
iodine by passage through a thiosulfate scrubber and washing with thio-
sulfate solution.

b. Administration of the Radioactive Gas. The gas, whose partition co-
efficient between water and gas at room temperature is approximately

0.15, is dissolved in Tyrode's solution in amounts to yield a concentration of 30 to 40 microcuries per ml. Ten ml. of this solution is injected continuously at a constant rate over a 1-minute period through a plastic catheter into the femoral vein of a cat. Since the specific activity of the gas is high, e.g., approximately 250 microcuries per ml., the administration of the 300 to 400 microcuries required by the procedure is associated with insufficient molecular quantities of gas to produce any pharmacological effects.

An alternative route of administration of the radioactive gas is by inhalation through a closed circuit rebreathing system. Although this technique is more efficient as regards the quantity of radioactive gas required, it is more cumbersome because of the more elaborate apparatus involved.

c. *Determination of the Arterial Concentration.* During the 1-minute period of administration of the gas, arterial blood is drawn at a constant rate of 10 ml. per minute from a catheterized femoral artery through a helical glass tube fixed in the well of a well-type scintillation counter. The counting rate from the radioactivity in the blood in the helix is recorded continuously by means of a count rate meter and Speedomax recorder. Radioisotope concentration in the arterial blood is determined from the counting rate by calibration of the entire arterial monitoring system with standard radioactive iodide solutions. Corrections for the time delay caused by dead space, for the effects of washout of the entire catheter-helix system, and for instrument lag have been experimentally determined and are appropriately applied.

It was found that the relation between the true C_a and the indicated arterial concentration of the radioactive gas recorded by the Speedomax recorder, C_a', could be expressed by the equation:

$$C_a = C_a' + \frac{1}{r}\frac{dC_a'}{dt} \tag{8}$$

in which r is a rate constant which describes the lag in C_a'. The value of r was determined from a semilogarithmic plot of the record obtained when a constant concentration of radioactive iodide solution was suddenly drawn into the helix-catheter system at the same rate as was employed in the experiments. By substituting Eq. (8) in Eq. (7), the relation

$$\frac{(C_i)_T}{\lambda} = k \int_0^T C_a' e^{-k(T-t)}(1 - k/r)\, dt + (k/r)(C_a')_T \tag{9}$$

was obtained in which $(C_a')_T$ is the value of C_a' at time T. By means of Eq. (9), it is possible to calculate the rate of blood flow directly from the arterial saturation curve drawn by the Speedomax recorder.

d. *Determination of Tissue Concentration.* At exactly 1 minute after the start of the administration of the radioactive gas and the sampling of the

femoral arterial blood, the cat is decapitated, and the head is immediately placed in liquid nitrogen and frozen. Several holes are drilled in the frozen head and these are filled with gelatin solutions of known concentrations of radioactive iodide. These serve as calibration standards, and they are made to span the range of the concentrations generally present in the cerebral tissues at the time of decapitation. When the calibration standards have been frozen, the head is sawed on a band saw into coronal sections about 5 mm. thick. Care is taken to keep the head from thawing during the sawing process. Kodak No-Screen X-ray films are closely applied the the surfaces of the frozen sections and exposed to them at the temperature of dry ice for approximately 12–36 hours.

The actual exposure time has been empirically related to the *average* radioisotope concentration in the arterial blood during the 1-minute experimental procedure. It has been found that with approximately 3 $\mu c./ml.$-hours exposure satisfactory radioautographs are generally obtained. Division of this factor by the average arterial concentration in $\mu c./ml.$ yields the actual exposure time in hours. Sample radioautographs are shown in Fig. 1. The circular areas of uniform density in the radioautographs represent the radioactive iodide containing gelatin standards. The marked variations in density among the areas, apparent in the films, indicate the concentration differences of the gas in the tissues of the sections which were lying immediately adjacent to them. Since the radioautographs result almost entirely from the effects of the β-radiation, they reflect the tissue concentration only to a depth of about 2 mm. below the surface, the approximate infinite thickness layer for the β-particles of I^{131}.

The tissue concentrations, $(C_i)_T$, of the various cerebral structures apparent on the surface of the head sections are quantitatively determined from the radioautographs by measurement of the optical density of the areas in the films which represent them. The densitometer employed in these measurements permits a resolution of approximately 1 mm. Calibration of the optical density readings in units of radioisotope concentration is obtained from a curve relating the optical density of the gelatin standards to their known concentration of I^{131}.

Similar radioautographs have been made after the injection of I^{131}-tagged serum albumin which does not leave the vascular space. These demonstrate that the radioautographs obtained in the blood flow studies with the I^{131}-tagged trifluoroiodomethane are not measurably affected by the quantity of isotope in the blood in the tissues but represent almost entirely the concentrations in the extravascular tissue spaces. They reflect, therefore, the effects of tissue blood flow and not tissue blood volume, as is the case when the nondiffusible serum albumin is employed as the tracer.

e. Determination of the Tissue:Blood Partition Coefficients. The partition
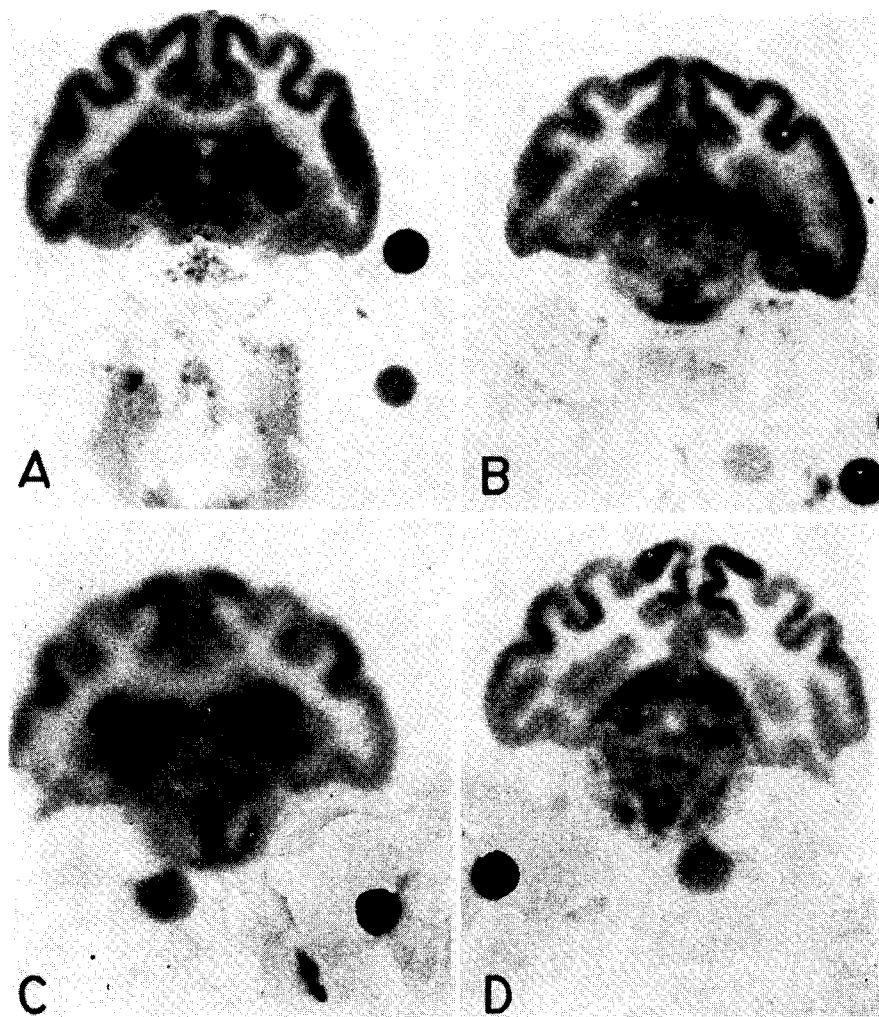
FIG. 1. Radioautographs obtained from cats that had been conscious. A and B from blindfolded cats; C and D from cats during photic stimulation. A and C are from comparable coronal sections, as are B and D. The tissue concentrations are those present following 1 minute of infusion of the CF_3I^{131} solution and are determined chiefly by blood flow and to a slight extent by the solubility in the tissues. The degree of density, therefore, reflects mainly the blood flow to the area. Circular areas of uniform density in lower portions of the radioautographs were made by calibration standards. See text. (From Sokoloff (26).)

coefficients for the radioactive gas between the various brain tissues and the blood differ among cats. It is, therefore, necessary to determine them in each animal on which blood flow studies are made. The variation results mainly from differences in the solubility of the gas in the blood whose composition, particularly the hematocrit, varies considerably among cats. On the other hand, the solubility of the gas in the brain, although varying from one tissue to another, is relatively constant for each tissue from cat to cat. Therefore, once the tissue:gas partition coefficients have been determined for each cerebral tissue, it is necessary only to measure the blood:gas partition coefficient for any subsequent animal in order to calculate its tissue:blood partition coefficients. For example, division of each of the tissue:gas partition coefficients by the blood:gas partition coefficient yields the tissue:blood partition coefficients needed in the determination of blood flow.

In Table I are listed the tissue:gas partition coefficients for a number of tissues of the brain. This is the same as the relative solubility of trifluoro-iodomethane in tissue with respect to room air at 37°C. They are the mean values obtained from a series of cats in the following manner. The cats were permitted to breathe through a closed circuit rebreathing system a mixture of the radioactive gas in room air for a period of about 1 hour. After this amount of time, the arterial concentration of the gas becomes approximately constant, and all the cerebral tissues are more or less in equilibrium with the blood. At this point, a sample of arterial blood was drawn, the cat was decapitated, and the head frozen in liquid nitrogen. The concentrations of radioactive gas in the various cerebral tissues were then determined by means of the radioautographic technique previously described. Typical radioautographs of these studies are illustrated in Fig. 2. The concentration of the gas in the arterial blood sample was measured in a well-type scintillation counter. The ratios of tissue to blood concentrations yield the tissue:blood partition coefficients.

Samples of blank blood drawn before the onset of administration of the gas were allowed to equilibrate in glass tubes with a mixture of radioactive gas in room air at 37°C. The equilibrium concentrations of the radioactive gas in the blood and gas phases were then measured with a scintillation counter, and the ratio of blood concentration to that in the gas yielded the blood:gas partition coefficient for the same cat. The tissue:gas partition coefficients were then calculated by multiplying each tissue:blood partition coefficient by the blood:gas partition coefficient of the same cat. The mean tissue:gas partition coefficients derived from this series (Table I) are the values from which the tissue:blood partition coefficients were calculated in the subsequent experiments on local blood flow on other cats. In each

of these experiments the blood:gas partition coefficient was measured as above and divided into the tissue:gas partition coefficients in Table I to obtain the tissue:blood partition coefficients in each experimental cat.

f. Calculation of Blood Flow. The methods for measuring all the experi-

TABLE I

Brain: Gas Partition Coefficients[a] for Trifluoroiodomethane in the Central Nervous System

Tissues	Mean	Standard error	Number of cats
Blood	0.66	0.02	9
Cerebral gray	0.57	0.03	8
Cerebellar gray	0.63	0.04	9
Olfactory gray	0.60	0.04	8
Caudate	0.63	0.03	9
Amygdala and basal ganglia	0.61	0.03	5
Hippocampus	0.61	0.03	8
Thalamus	0.82	0.05	7
Hypothalamus	0.75	0.04	9
Reticular substance	1.00	0.04	9
Medial geniculate	0.91	0.04	7
Lateral geniculate	0.86	0.05	7
Superior colliculus	0.88	0.05	7
Inferior colliculus	0.85	0.05	4
Cerebral white	1.05	0.03	5
Cerebellar white	1.11	0.05	9
Cord gray	0.86	0.05	5
Cord white	1.01	0.04	8
Pyramidal tract	1.14	0.06	7
Optic tract	1.06	0.04	5
Pons gray	0.85	—	2
Pons white	1.16	0.09	5
Cerebellar nuclei	0.98	—	2
Vestibular nuclei	1.05	0.06	6
Superior olive	1.01	0.05	3

[a] Determined at 37°C.

mentally determined quantities in Eq. (7) or Eq. (9) have been described. Remaining is the problem of solving this equation for k, from which, since it equals $F/\lambda W$, the blood flow per gram of tissue per minute, F/W is obtained directly, by multiplication with the appropriate λ. The solution is most readily accomplished by an analog computer, but the following graphical method has been found to be satisfactory. $\dfrac{(C_i)_T}{\lambda}$, the left side
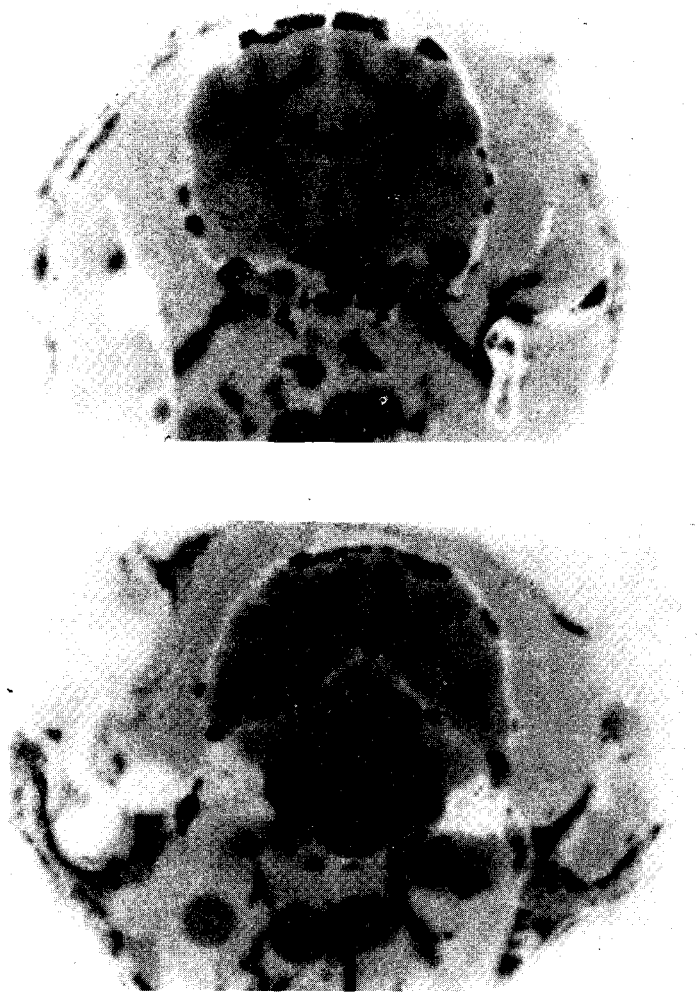
FIG. 2. Radioautographs obtained from cats allowed to breathe an air-CF_3I^{131} mixture for 1 hour. The tissues are then in equilibrium with the arterial blood. The tissue concentration is not dependent on blood flow but on the solubility of the gas in the tissues. Since trifluoroiodomethane is more soluble in white matter than in gray, the white areas appear darker than the gray in these radioautographs. The circular areas of uniform density in the lower portions of the radioautographs are made by calibration standards. See text.

of the equation, is calculated for a wide range of assumed values of k. Integration of the expression

$$\int_0^T C_a e^{-k(T-t)}\, dt$$

is accomplished by Simpson's Rule after division of the experimentally determined arterial curve over the 1-minute period, 0 to T, into 10 equal time periods. When the calculated values for $\dfrac{(C_i)_T}{\lambda}$ are plotted against the assumed values of k, a smooth curve results, from which, for every tissue whose $\dfrac{(C_i)_T}{\lambda}$ has been experimentally measured, the true k can be obtained. Multiplication of k by the appropriate λ then yields F/W, the blood flow per unit weight of tissue per minute.

III. RESULTS

1. Normal Values

The initial application of the method has been in the determination of the normal, conscious, resting values of blood flow in the individual regions of the cat's brain. In order to maintain the cats in as close to the physiological state as possible during the experimental situation, the following procedure was adopted. The femoral arterial and venous catheters were inserted while the cats were under divinyl ether anesthesia. Before closure, the operative wounds were infiltrated with 1 % procaine solution in order to maintain local analgesia after the cessation of the general anesthesia.

While still anesthetized, the cats were enveloped by partially filled sand bags which were carefully molded to the contours of their bodies. When the air in the plastic bags was evacuated by vacuum suction, they became hard, rigid, and inflexible, and restrained the cats as effectively as a plaster cast. Following this immobilization, the divinyl ether administration was discontinued, and at least 1 hour was allowed for recovery from the effects of the anesthesia. At this point, the 1-minute period of radioactive gas injection and arterial blood sampling was begun and was followed by an almost instantaneous decapitation by means of a guillotine driven by compressed air.

The results are presented in Table II. The values for blood flow in the unanesthetized or "normal" series fall into two general groups: those for gray matter and those for white matter. The blood flow in the white matter varied between 0.14 cc./gm./min. in the tracts of the spinal cord to 0.27 cc./gm./min. in the optic tract. Gray matter was found to have a considerably higher blood flow; the values ranged from 0.59 cc./gm./min. in

TABLE II
Local Cerebral Blood Flow in the Cat

Structure	Blood flow (cc./g./min.) (Mean ± S.E.)	
	Conscious (10 cats)	Light thiopental anesthesia (11 cats)
I. Superficial cerebral structures		
Cortex:		
Sensory-motor	1.38 ± 0.12	0.65 ± 0.07[a]
Auditory	1.30 ± 0.05	0.72 ± 0.07[a]
Visual	1.25 ± 0.06	0.77 ± 0.09[a]
Miscellaneous-association	0.88 ± 0.04	0.67 ± 0.06[a]
Olfactory	0.77 ± 0.06	0.62 ± 0.07
White matter	0.23 ± 0.02	0.26 ± 0.04
II. Deep cerebral structures		
Medial geniculate ganglion	1.22 ± 0.04	0.81 ± 0.09[a]
Lateral geniculate ganglion	1.21 ± 0.08	0.79 ± 0.07[a]
Caudate nucleus	1.10 ± 0.08	0.91 ± 0.11
Thalamus	1.03 ± 0.05	0.71 ± 0.09[a]
Hypothalamus	0.84 ± 0.05	0.55 ± 0.06[a]
Basal ganglia and amygdala	0.75 ± 0.03	0.58 ± 0.05[a]
Hippocampus	0.61 ± 0.03	0.59 ± 0.04
Optic tract	0.27 ± 0.02	0.22 ± 0.08
III. Midbrain and pons		
Inferior colliculus	1.80 ± 0.11	1.41 ± 0.14[a]
Superior olive	1.17 ± 0.13	1.56 ± 0.27
Superior colliculus	1.15 ± 0.07	0.82 ± 0.10[a]
Pontine gray	0.88 ± 0.04	0.61 ± 0.03[a]
Reticular formation	0.59 ± 0.05	0.49 ± 0.06
Pontine white	0.24 ± 0.02	0.31 ± 0.04
IV. Cerebellum, medulla, and spinal cord		
Cerebellum:		
Nuclei	0.79 ± 0.05	0.56 ± 0.08[a]
Cortex	0.69 ± 0.04	0.57 ± 0.05[a]
White matter	0.24 ± 0.01	0.29 ± 0.06
Medulla:		
Vestibular nuclei	0.91 ± 0.04	0.84 ± 0.10
Cochlear nuclei	0.87 ± 0.07	0.99 ± 0.14
Pyramids	0.26 ± 0.02	0.28 ± 0.03
Spinal cord:		
Gray matter	0.63 ± 0.04	0.53 ± 0.07
White matter	0.14 ± 0.02	0.15 ± 0.06

[a] Statistically significantly different from conscious control values (p < 0.05).

the brainstem and midbrain reticular formation to 1.8 cc./gm./min. in the inferior colliculi. The circulation in the inferior colliculi was found to be the most rapid of all the cerebral tissues thus far studied, but it is possible that there are structures too small to be studied by this technique whose perfusion rates might be higher.

Small structures might be missed in these studies because they were buried in the depths of the tissue slices and therefore not represented in the radioautographs or were represented by areas in the films less than 1 mm. in diameter, the limit of resolution of the densitometric measurements. Next to the inferior colliculi, the highest values for blood flow were observed in certain areas of the cerebral cortex. If parts of the cerebral cortex are sufficiently devoted to specific sensory modalities to justify their classification according to such functions, then it is the somatosensory, auditory, and visual areas which are rapidly perfused; the values for blood flow obtained in them are considerably higher than in the olfactory and other cortical areas.

2. Effects of Thiopental Anesthesia

Similar studies were conducted in cats lightly anesthetized by thiopental in order to ascertain the pattern of effects of such anesthesia on the blood flow of the various structures of the brain. Technically these experiments were identical to those performed on the conscious cats except that instead of allowing them to regain consciousness, they were maintained in a lightly anesthetized state after the administration of divinyl ether was discontinued. Thiopental was injected intravenously as required to maintain a level of anesthesia at which the corneal reflex was still barely active during the period of the experiment.

In Table II are presented the results obtained in the anesthetized series as compared to those in the unanesthetized cats. In general, the effects of thiopental anesthesia were to reduce blood flow and to diminish the variation among the various cerebral structures so that they all had more nearly the same circulation. This effect is most apparent in the cortical areas where the contrasts, which are so evident in the conscious state, are abolished. The marked difference in the rates of blood flow between white and gray matter, however, remains. In view of the effects of anesthesia on nervous functions, these results, particularly those in the cerebral cortical areas, lend support to the hypothesis that local cerebral blood flow is regulated by the local functional activity.

3. Effects of Altered Tensions of Oxygen and Carbon Dioxide in the Inspired Air

The respiratory gases, carbon dioxide and oxygen, are the most potent agents for altering the cerebral blood flow. Their tensions in the blood

and cerebral tissues are generally believed to be the chief physiological mechanism for the intrinsic regulation of the cerebral circulation. The effects of altering their concentrations in the inspired air were investigated for two reasons: (1) to test the ability of the method to demonstrate the changes known to be caused by such altered gas tensions from studies of the overall cerebral circulation; (2) to determine the uniformity of their effects in the various portions of the brain. Two inspired air mixtures were employed, one with a high carbon dioxide (5 % CO_2, 21 % O_2, and 74 % N_2) and the other with a low oxygen (10 % O_2, 90 % N_2) concentration, both of which are known to raise markedly the cerebral blood flow (16). The studies were performed in conscious, unanesthetized cats. The inspired gas mixture was allowed to flow at a rate of 15 liters per minute through a Plexiglas box which enclosed the head of the animal. A 15-minute period of equilibration with the inspired air was permitted before the measurements were made. Otherwise the experimental procedure was exactly as previously described. Similar control experiments were done on cats breathing room air.

The results of these studies (8) are summarized in the bar graphs in Fig. 3. Increases in blood flow were observed with both gas mixtures in all the cerebral structures studied. The vast majority of the changes were statistically significant ($p < 0.05$); a few that were not would in all likelihood have been found to be so had the series been larger. In general, both 5 % CO_2 and 10 % O_2 caused greater increases in blood flow in gray matter than in white matter. With the 5 % CO_2, the mean increases were 67 % in gray matter and 54 % in white matter; with the 10 % O_2, they were 92 % in gray matter and 65 % in white matter. The only structures in which 5 % CO_2 caused statistically significant increases in blood flow of greater
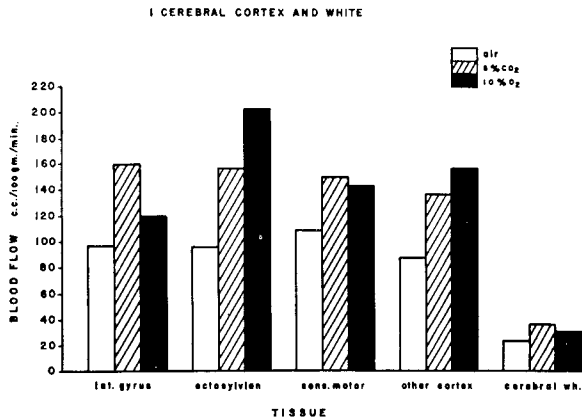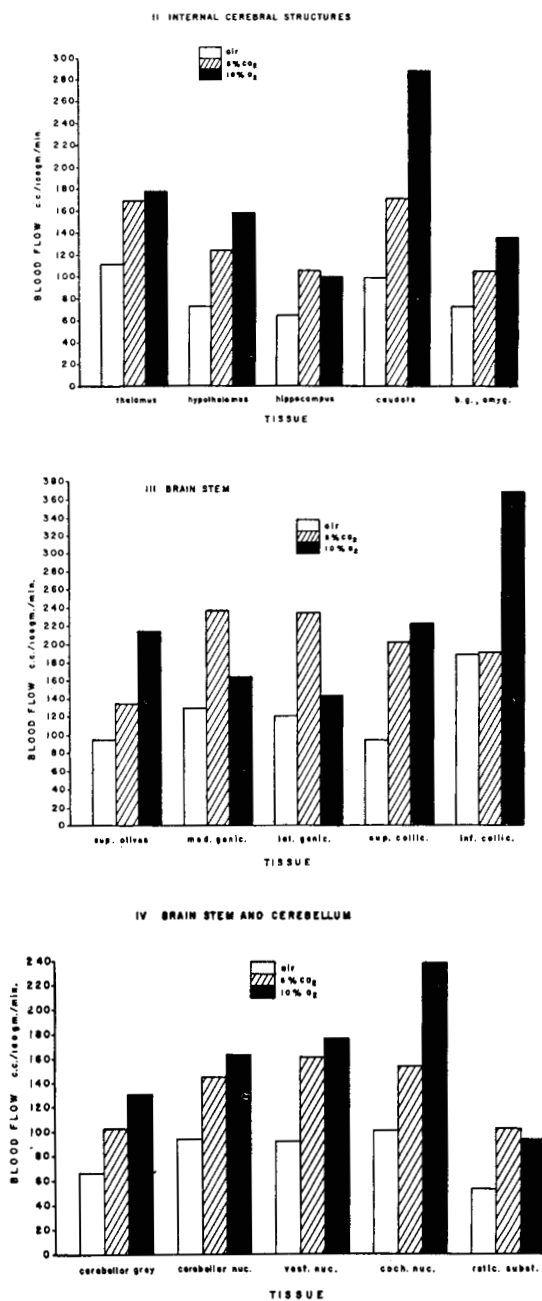

FIG. 3.

FIG. 3. Effect of 5% CO_2 and 10% O_2 on local circulation of cat brain.

magnitude than did 10% O_2 were the lateral and medial geniculate nuclei. In most other areas the low oxygen mixture caused the greater increases in blood flow.

4. Effects of Visual Stimulation

In view of the possible relationship between local cerebral blood flow and local functional activity, visual stimulation might be expected to increase the blood flow in those areas of the brain associated with this function. Preliminary studies (26) indicate that such is the case. In conscious, unanesthetized cats whose eyes had been previously atropinized, retinal stimulation was achieved by means of flashes of light at a rate of 6 per second and at the maximum intensity available from a Grass photic stimulator. The visual stimulation was maintained continuously for a period of 5 minutes immediately preceding and for the 1-minute period during the experimental run.

In the few experiments of this type thus far performed, it has been observed that blood flow appears to be increased in areas of the brain involved in visual functions, e.g., the lateral gyri, lateral geniculate nuclei, and the superior colliculi. The areas corresponding to these structures in the radioautographs in Fig. 1 are seen to be more prominent in the experimental studies than in similar control studies performed on blindfolded cats. Since the optical density in these radioautographs represents the concentration of the gas in the tissue which in turn reflects chiefly the blood flow to the tissue, it is apparent that these structures have an accelerated rate of perfusion during visual stimulation. Quantitation of the changes has not yet been performed.

IV. SUMMARY

A method for the simultaneous quantitative determination of blood flow in the individual structures of the cat's brain has been presented. Its theoretical basis has been described, and the results of early investigations designed to test its capabilities as well as to contribute to useful physiological information have been discussed. These results are qualitatively and quantitatively very similar to what might be expected on the basis of studies of the blood flow of the brain as a whole and suggest that the method is valid and reliable. It is a method which involves a large number of operations, and extreme care and attention to details are necessary in its application to avoid an accumulation of random errors which may cause so great a variation in results as to preclude significant interpretation. With carefully controlled technique, however, it appears to be capable of providing data which may aid in answering some of the current questions about the regulation of the regional cerebral circulation.

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